Thrombotic Cardiovascular Events Associated with NSAID Use: Regulatory History and Results of Literature Search (RCTs)

Joint Meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee

February 10-11, 2014

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Agenda

- Regulatory history
- Current NSAID class labeling
- PRECISION trial
- Literature search
- Results- individual randomized controlled trials (RCTs)
- EMA- recent actions regarding NSAIDs

Nationally Estimated Number of Prescriptions Dispensed and Unique Patients Receiving Selected NSAIDs through U.S. Outpatient Retail Pharmacies, October 2011-September 2012, Cumulative

	Prescriptions*	Patients†
IBUPROFEN	31,269,304	18,584,650
MELOXICAM	18,511,986	7,453,500
NAPROXEN	17,118,827	10,474,084
DICLOFENAC	11,289,892	5,209,514
CELECOXIB	7,754,283	2,348,622
INDOMETHACIN	2,962,239	1,719,545
NABUMETONE	2,734,992	1,276,096
ETODOLAC	2,165,687	1,155,035
PIROXICAM	749,634	351,495
SULINDAC	633,502	285,428
KETOPROFEN	330,720	184,021
FLURBIPROFEN	232,830	116,120
TOLMETIN	21,442	8,600
FENOPROFEN	20,590	9,800
MECLOFENAMIC ACID	16,353	10,204

**Source: IMS Health, National Prescription Audit (NPA) , Extracted September 2013*

†Source: IMS Health, Total Patient Tracker (TPT), Extracted November 2012

Feb 2005 Joint Meeting of AAC and DSaRM AC

Convened to discuss the risk of cardiovascular thromboembolic events with COX-2 selective NSAIDs and non-selective NSAIDs (e.g., ibuprofen, naproxen, diclofenac, and others) that occurred in large RCTs of COX-2 selective NSAIDs.

Anti-platelet Trialist Collaboration (APTC) Composite Endpoint

- Deaths- vascular and unknown cause
- Non-fatal MI
- Non-fatal stroke (ischemic & hemorrhagic)

(does not include unstable angina, transient ischemic attack & peripheral vascular events)

Antiplatelet Trialists Collaboration. Collaborative overview of randomized trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ. 1994;308:81–106.

Summary of Results of Large RCTs

- Provided as a reminder of the data that was discussed at the Feb 2005 AC
- The APTC composite endpoint was not the primary endpoint in all the studies; as such, RR estimates and confidence intervals are not available for all studies

Rofecoxib – Large RCTs

Trial name	Indication	Study drugs	APTC endpoint n (rate/100 pyr) **Study drug**	APTC endpoint n (rate/100 pyr) **Comparator**	Relative Risk (95% CI)
VIGOR	Rheumatoid arthritis (median Tx 9 mos)	rofecoxib 50 mg (n = 4047) vs. naproxen 500 mg bid (n = 4029)	35 (1.30)	18 (0.67)	1.94
ADVANTAGE	Osteoarthritis (12 weeks)	rofecoxib 25 mg (n = 2785) vs. naproxen 500 mg bid (n = 2771)	10 (1.56)	7 (1.11)	1.41
091 078	Alzheimer's Disease: Treatment/ prevention (3 years)	rofecoxib 25 mg (n = 1069) vs. placebo (n = 1074)	32 (1.88)	40 (2.07)	0.91
APPROVe	Prevent colorectal adenomas (3 years)	rofecoxib 25 mg (n = 1287) vs. placebo (n = 1299)	34 (1.11)	18 (0.54)	2.06 (1.16, 3.64)
VICTOR	Prevent recurrence Stage II/III colorectal Ca (median Tx 7.4 mos)	rofecoxib 25 mg (n = 1167) vs. placebo (n = 1160)	9 (0.97)	6 (0.61)	1.42 (0.50, 4.03)

Celecoxib- Large RCTs

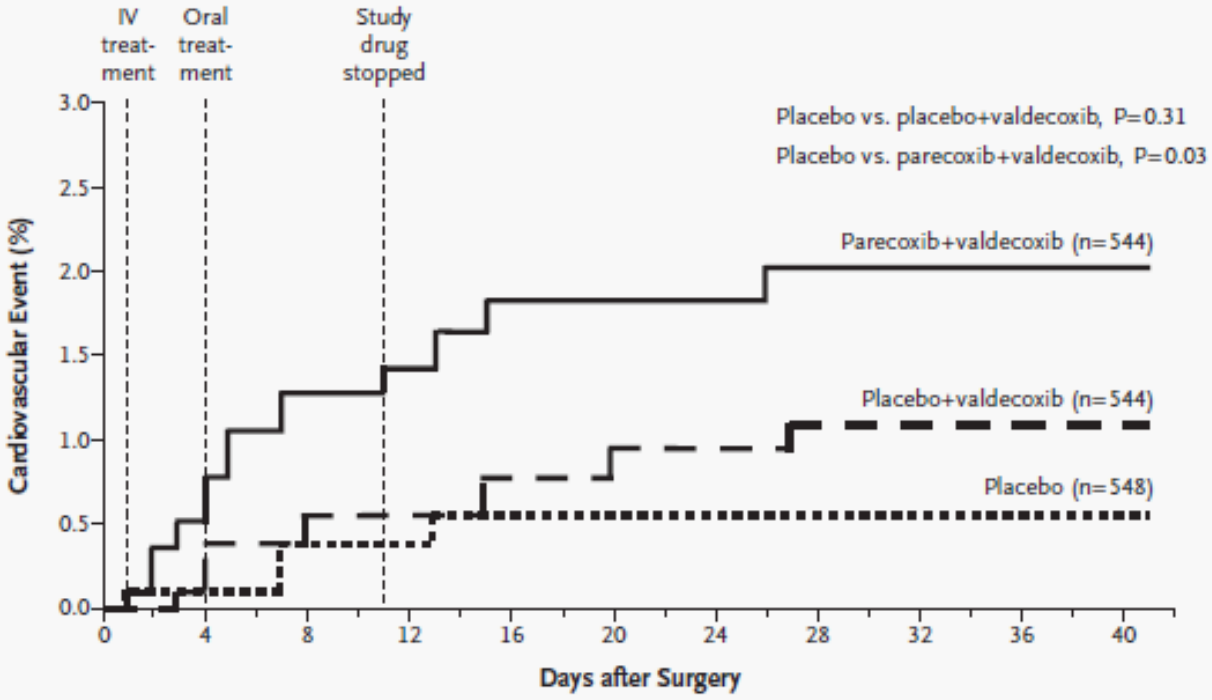
Trial name	Indication	Study drugs	APTC endpoint n (rate/100 pyr) **Study drug**	APTC endpoint n (rate/100 pyr)* **Comparator**	Relative Risk (95% CI)
CLASS	Rheumatoid arthritis/ Osteoarthritis (median tx 6-9 mos)	celecoxib 400 mg bid (n = 3987) vs. diclofenac 75 mg bid (n = 1996) or ibuprofen 800 mg tid (n = 1985)	34 (0.9%)	(diclofenac) 15 (0.8%) (ibuprofen) 20 (1.0%)	
APC	Prevent colorectal Adenomas (3 years)	celecoxib 200 mg bid (n = 685) or celecoxib 400 mg bid (n = 671) vs. placebo (n = 679)	17 (0.82) 20 (0.99)	6 (0.29)	2.8 (1.1, 7.2) 3.4 (1.4, 8.5)
PreSAP	Prevent colorectal Adenomas (3 years)	celecoxib 400 mg q day (n = 933) vs. placebo (n = 628)	21 (0.86)	12 (0.72)	1.2 (0.6, 2.4)
ADAPT	Prevent Alzheimer's disease (AD) in subjects with family hx of AD (median tx 14-16 mos)	celecoxib 200 mg bid (n = 726) vs. naproxen 220 mg bid or placebo (n = 1083)	17 (celecoxib) 23 (naproxen)	22 placebo)	1.14 (0.61, 2.15) 1.57 (0.87, 2.81)

*except where otherwise noted as %

Other Coxibs – Large RCTs

Trial name	Indication	Study drugs	APTC endpoint n (rate/100 pyr) **Study drug**	APTC endpoint n (rate/100 pyr) **Comparator**	Relative Risk (95% CI)
EDGE/MEDAL	Rheumatoid arthritis/ Osteoarthitis (mean tx 18 mos)	etoricoxib 60–90 mg (n = 17412) vs. diclofenac 150mg (n = 17289)	231 (0.87)	232 (0.91)	0.96 (0.8, 1.2)
TARGET	Osteoarthritis (1 year)	lumiracoxib 400 mg (n = 4741) vs. naproxen 500 mg bid (n = 4730) AND lumiracoxib 400 mg (n = 4376) vs. ibuprofen 800 mg tid (n = 4397)	40 (1.1) 19 (0.59)	27 (0.76) 23 (0.74)	1.46 (0.89, 2.37) 0.76 (0.41, 1.40)

Kaplan-Meier Estimates of the Time to a Cardiovascular Event



No. at Risk

Parecoxib+valdecoxib	544	541	537	536	534	534	534	533	519	495	476
Placebo+valdecoxib	544	543	542	541	540	540	539	538	518	478	454
Placebo	548	547	546	546	545	545	545	545	525	489	475

Cardiovascular events included cardiac (myocardial infarction, severe myocardial ischemia, sudden death from cardiac causes, or unexpected death without an identifiable non-cardiac cause within 60 minutes after the onset of symptoms), cerebrovascular, and peripheral vascular events. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, Boyce SW, Verburg KM. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005;352:1081-91.

Feb 2005 Joint AC Meeting- Conclusions

- The committee opined that there appeared to be a class effect for cardiovascular risk associated with the three approved COX-2 selective NSAIDs (i.e., rofecoxib, celecoxib, and parecoxib/valdecoxib);
- There was less agreement with regard to the non-selective NSAIDs, but the general recommendation was that similar warnings be applied to these drug as well.

April 2005 FDA Action

Based on assessments of cardiovascular (CV) risk in RCTs evaluating the efficacy of COX-2 selective and non-selective NSAIDs in OA/RA/chemoprevention indications, and the discussion of such studies at the Feb 2005 AC meeting, FDA made the following conclusions

- The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data do not permit a rank ordering of these drugs with regard to CV risk.
- Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.
- Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.

April 2005 FDA Action (2)

- Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.
- Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately post-operative from coronary artery bypass (CABG) surgery).
- Valdecoxib is associated with an increased rate of serious and potentially life-threatening skin reactions compared to other COX-2 selective agents and is the only NSAID with a boxed warning for this adverse event in its approved package insert. In the absence of any demonstrated advantage over nonselective NSAIDs, the overall benefit versus risk profile for valdecoxib is unfavorable for marketing.

April 2005 FDA Action (3)

Based on these conclusions, the following actions were taken:

- Withdrawal of valdecoxib
- Revision of the labeling of all NSAIDs to include the following
  - A boxed warning highlighting the potential for increased risk of CV events with these drugs and the well-described, serious, and potentially life-threatening gastrointestinal (GI) bleeding associated with their use.
  - Addition of a contraindication for use in patients immediately post-operative from CABG surgery.
  - Dispensing of a Medication Guide with every prescription NSAID at the time it is dispensed to better inform patients about the CV and GI risks.
- Revision of non-prescription (OTC) NSAID labeling to include more specific information about the potential GI and CV risks, and information to assist consumers in the safe use of those drugs.
- Agency request for sponsors of non-selective NSAIDs to conduct and submit a comprehensive review and analysis of available controlled clinical trial databases to further evaluate the potential for increased CV risk.

European Medicines Agency Recommendations: 2005-6

- COX-2 selective NSAIDs
  - Contraindications stating that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
  - Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking
  - Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment
- Non-selective NSAIDs
  - Non-selective NSAIDs are important treatments for arthritis and other painful conditions.
  - It cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events especially when used at high doses for long-term treatment.
  - The overall benefit-risk balance for non-selective NSAIDs remains favourable when used in accordance with the product information, namely on the basis of the overall safety profile of the respective non-selective NSAID, and taking into account the patient's individual risk factors (e.g. gastrointestinal, cardiovascular and renal).

Prescription NSAID Labeling

Boxed Warning

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).

- TRADENAME is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See **WARNINGS**).

Prescription NSAID Labeling
Warning Section

- Cardiovascular Thrombotic Events
  - Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal.
  - All NSAIDs, both COX-2 selective and nonselective, may have a similar risk.
  - Patients with known CV disease or risk factors for CV disease may be at greater risk.

Prescription NSAID Labeling
Warning Section (2)

- Cardiovascular Thrombotic Events (cont'd)
  - To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible.
  - Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms.
  - Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

Prescription NSAID Labeling
Warning Section (3)

- Cardiovascular Thrombotic Events (cont'd)
  - There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see WARNINGS, GI Effects).
  - Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see CONTRAINDICATIONS).

OTC Product Labeling Regarding Cardiovascular Risk

- Do not use
  - right before or after heart surgery
- Ask a doctor before use if
  - you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
  - you are taking a diuretic
- Ask a doctor or pharmacist before use if you are
  - under a doctor's care for any serious condition
  - taking any other drug
  - (ibuprofen) taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin

OTC Labeling Regarding Cardiovascular Risk (2)

- When using this product
  - the risk of heart attack or stroke may increase if you use more than directed or for longer than directed
- Stop use and ask a doctor if
  - any new symptoms appear
- Directions
  - do not take more than directed
  - the smallest effective dose should be used

Evaluations Subsequent to 2005 Action

- Review of submissions from development programs of non-selective NSAIDs did not provide additional actionable data
- FDA recognized the need for comparative data on CV thrombotic risk with COX-2 selective and non-selective NSAIDs
- Postmarketing commitment requested of Pfizer for comparative trial of celecoxib vs. naproxen and ibuprofen

PRECISION Trial

Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen

- Randomized, double-blind, three-arm, non-inferiority study to compare the cardiovascular risk of celecoxib, ibuprofen and naproxen in OA and RA in patients at high risk for cardiovascular disease
  - Patients stratified based on diagnosis of OA, RA and ASA use
- The treatment arms
  - Celecoxib 100-200mg BID
  - Ibuprofen 600-800mg TID
  - Naproxen 375-500mg BID
- Primary endpoint: APTC composite outcome
- The trial size and duration are event-driven but all patients must have 18 months follow-up or longer
- Original planned sample size ~20,000 total patients and 762 APTC cardiovascular events

PRECISION Trial

- Original date expected for completion of commitment: December 2013
- Updated status information
  - Patient accrual rate: ~200 patients per month
  - Enrollment as of 05 December 2013:
    - 22,278 patients randomized

    (20,000 patients original total planned enrollment)
  - Revised total planned enrollment:
    - 24,200 - 28,400

Continued Monitoring of the Issue

- In summer of 2011, a study published by Schjerning-Olsen et al in Circulation demonstrating the association of death and recurrent myocardial infarction (MI) in patients with prior MI occurring as early as one week after starting NSAIDs came to the attention of the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
- The current NSAID labeling does not specify time to event for the CV risk
- DAAAP requested consults from the Division of Cardiology and Renal Products and the Division of Epidemiology

Literature Search

- A search for NSAIDs and cardiovascular events was run in English in Pubmed (8-11-11) and EMbase databases (8-29-11) for articles published within the last 5 years
  - The results included: commentaries, clinical trials, meta-analyses, review articles, and epidemiologic studies
- A follow-up search was run in March 2012 to pick up any new studies published in the six months since the initial search
  - Very few additional studies identified

Literature Review Findings

- Individual epidemiological studies and meta-analyses of epidemiological studies will be presented by FDA's Dr. Mosholder
- Many of the published epidemiological cohort studies come from the Danish National Registry
  - Dr. Gislason will be presenting those
- Findings from individual randomized controlled trials will be summarized here

Coxib and Traditional NSAID (tNSAID) trialists' (CNT) Collaboration RCT Meta-analysis

- FDA learned of this project early in 2012 while it was under way
- Extension of a meta-analysis[1] of tabular data from randomized trials of a coxib vs placebo or a coxib vs tNSAID to include patient level data
- Published in The Lancet in May 2013
- Dr. Baigent, representing the CNT, will present the RCT meta-analysis results

[1]Kearney PM et al, BMJ 2006; 332: 1302-6

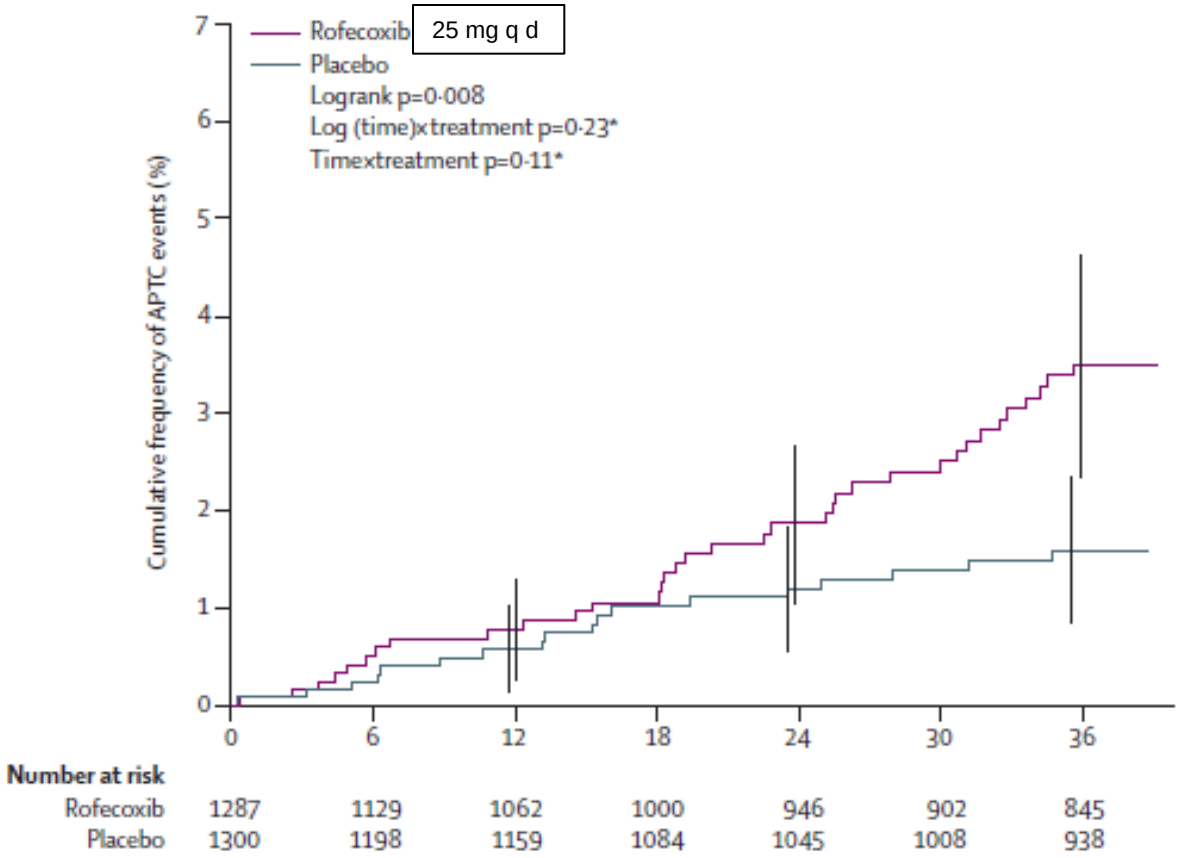
Literature Search: Individual RCTs

- Several publications were follow-up or final analyses of earlier RCTs
- Several studies were small and limited to specific patient populations (e.g., post stent placement or percutaneous coronary intervention) or used biomarkers or need for revascularization as endpoints.
- Some studies contributed information on time to event and risk in vulnerable populations

Time to Event

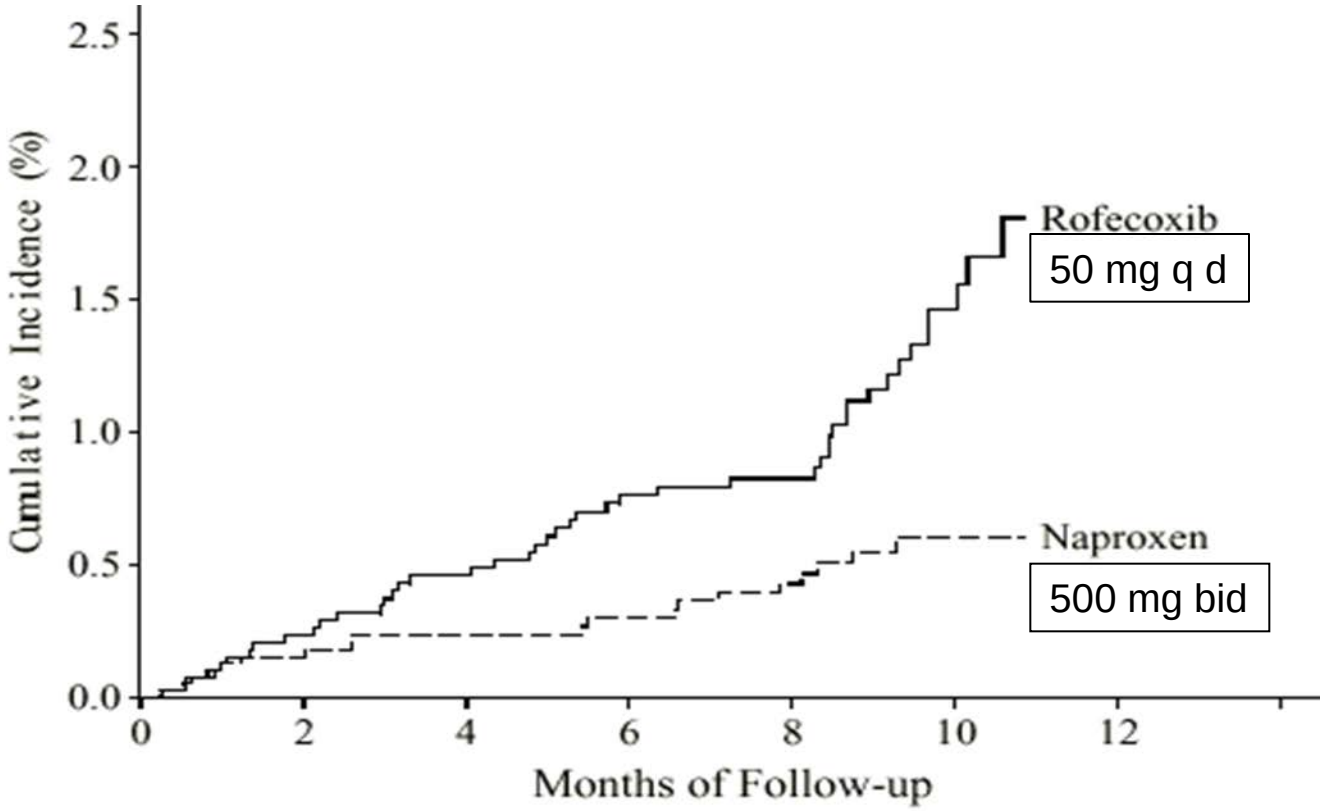
APPROVe

APTC Events on Treatment and Within 14 Days



Baron JA, Sandler RS, Bresalier RS, Lanas A, Morton DG, Riddell R, Iverson ER, Demets DL. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. Lancet. 2008;372:1756-64

VIGOR
Confirmed CV Thrombotic Events

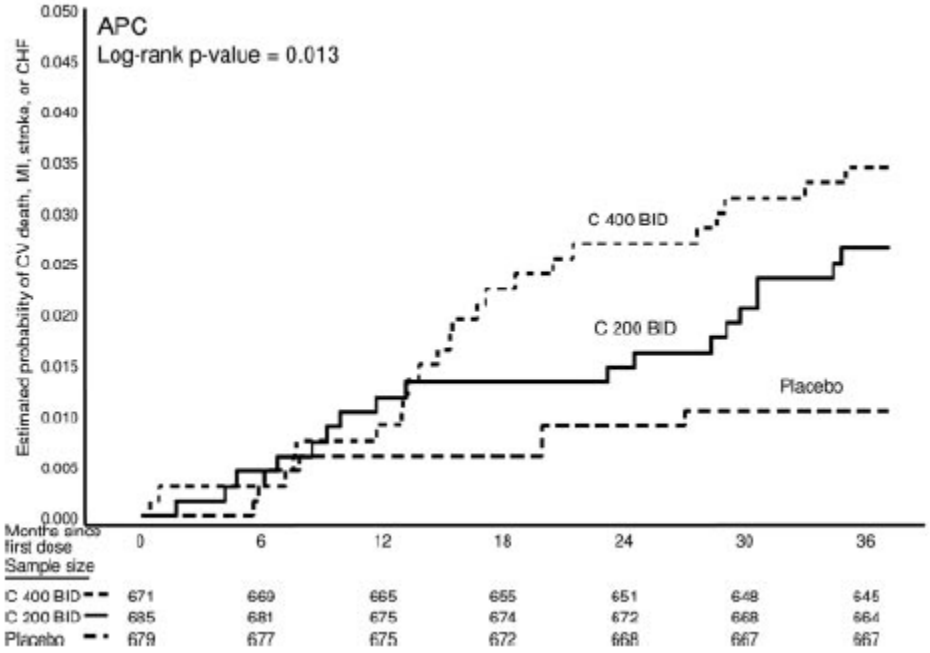


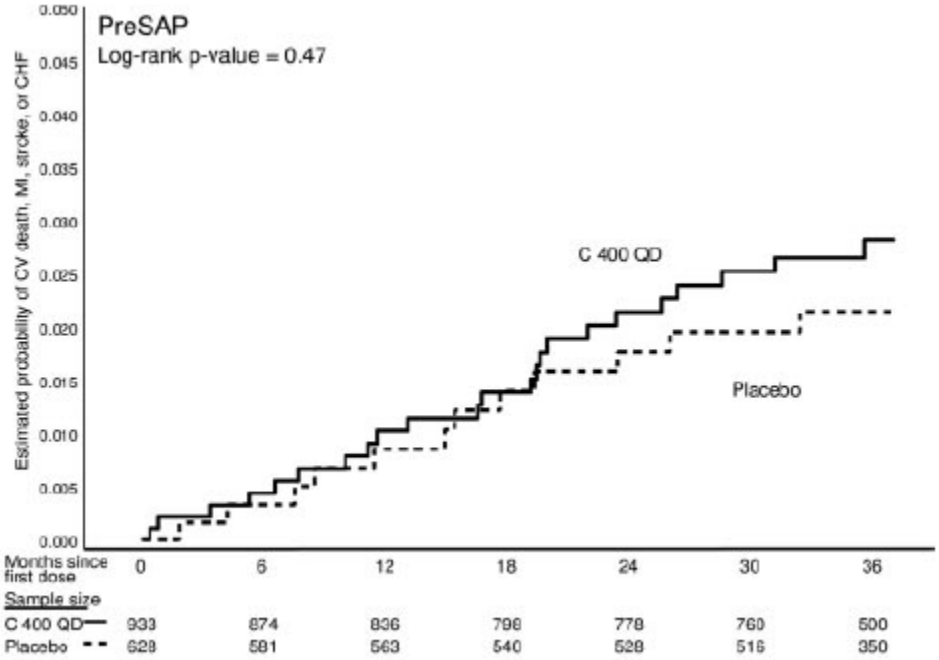
# at Risk						
Rofecoxib	n=4047	3643	3405	3177	2806	1067 531
Naproxen	n=4029	3647	3395	3172	2798	1073 514

Source: Dr. Villalba's slide presentation "Vioxx Cardiovascular Safety", February 16, 2005

APC/ PreSAP

Time to Event for CV Outcome*

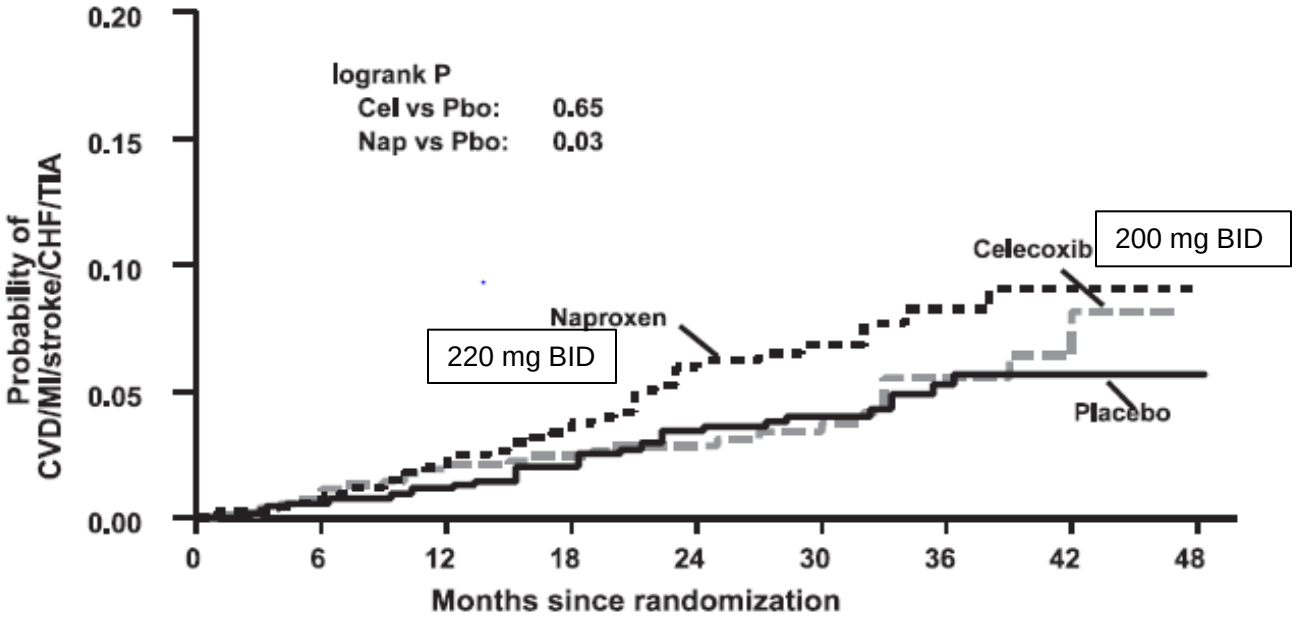




*Composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or heart failure

Solomon SD, Pfeffer MA, McMurray JJ, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation 2006;114(10):1028-35.

Alzheimer's Disease
Anti-Inflammatory Prevention Trial (ADAPT)
Time to Cardiovascular Death, MI, Stroke, CHF, or TIA



Number at risk									
Cel	726	677	599	516	396	273	148	55	4
Nap	719	665	587	498	384	262	150	57	5
Pbo	1083	987	868	762	591	405	235	90	6

Number of events								
Cel	8	6	2	2	3	4	2	1
Nap	6	10	7	11	2	3	0	1
Pbo	8	5	10	7	2	5	0	0

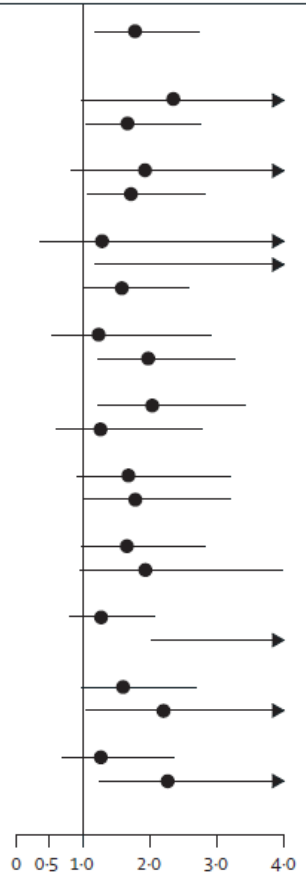
ADAPT Research Group (2006) Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). PLoS Clin Trials 1(7): e33. doi:10.1371/ journal.pctr.0010033

Vulnerable Populations (e.g., post-MI, CHF, risk factors for CVD)

APPROVe

Hazard Ratios for APTC Events by Subgroup

Baseline subgroup	Rofecoxib	Placebo	Unadjusted hazard ratio (95% CI)	p value for interaction
All patients	59/1287 (5%)	34/1300 (3%)	1·79 (1·17–2·73)	
Age at randomisation (years)				
≤59	17/675 (3%)	7/667 (1%)	2·40 (0·99–5·78)	0·50
>59	42/612 (7%)	27/633 (4%)	1·70 (1·05–2·75)	
Gender				
Female	15/483 (3%)	8/495 (2%)	1·96 (0·83–4·63)	0·81
Male	44/804 (5%)	26/805 (3%)	1·74 (1·07–2·82)	
Race				
Asian	5/81 (6%)	4/87 (5%)	1·31 (0·35–4·91)	
Black	9/70 (13%)	1/78 (1%)	9·42 (1·19–74·40)	0·12
White	44/1082 (4%)	28/1086 (3%)	1·61 (1·01–2·59)	
Body-mass index				
<25 kg/m^2	12/360 (3%)	10/370 (3%)	1·26 (0·54–2·91)	0·35
>25 kg/m^2	47/924 (5%)	24/922 (3%)	2·00 (1·22–3·27)	
Low-dose aspirin				
No	44/1074 (4%)	22/1096 (2%)	2·06 (1·23–3·43)	0·33
Yes	15/213 (7%)	12/204 (6%)	1·30 (0·61–2·78)	
Hypertension				
No	26/824 (3%)	16/854 (2%)	1·72 (0·92–3·20)	0·91
Yes	33/463 (7%)	18/446 (4%)	1·80 (1·01–3·20)	
Hypercholesterolaemia				
No	36/914 (4%)	23/962 (2%)	1·68 (0·99–2·83)	0·73
Yes	23/373 (6%)	11/338 (3%)	1·94 (0·95–3·98)	
Diabetes mellitus				
No	40/1172 (3%)	32/1189 (3%)	1·30 (0·81–2·06)	0·013
Yes	19/115 (17%)	2/111 (2%)	8·69 (2·02–37·38)	
Current smoker				
No	38/1007 (4%)	24/1015 (2%)	1·62 (0·97–2·70)	0·49
Yes	21/280 (8%)	10/285 (4%)	2·23 (1·05–4·74)	
High cardiovascular risk				
No	23/907 (3%)	19/958 (2%)	1·29 (0·70–2·36)	0·19
Yes	36/380 (9%)	15/342 (4%)	2·28 (1·25–4·17)	



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Hazard Ratio for Composite CV Outcome* in the Combined PreSAP and APC Trials Stratified by Baseline Risk Factors for CV Events

	Placebo, n/N (%)	Celecoxib, n/N (%)	Hazard Ratio (95% CI)	*P* for Interaction
Low-dose aspirin users				
Yes	7/319 (2.2)	25/570 (4.4)	2.1 (0.9–5.0)	0.8
No	12/988 (1.2)	39/1719 (2.3)	1.8 (1.0–3.5)	
History of cardiovascular events				
Yes	6/167 (3.6)	26/314 (8.3)	2.3 (0.9–5.6)	0.6
No	13/1140 (1.1)	38/1975 (1.9)	1.8 (0.9–3.3)	

*defined cardiovascular death, nonfatal MI, stroke, or heart failure

Solomon SD, Pfeffer MA, McMurray JJ, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation 2006;114(10):1028-35.

Recent Actions by the EMA

- October 2012: EMA releases assessment report for NSAIDs and cardiovascular risk
  - Naproxen may be associated with a lower risk for arterial thrombotic events than Cox-2 inhibitors and other NSAIDs, but a small risk cannot be excluded
  - Ibuprofen at high dose may be associated with an increased risk of thrombotic events, and the data do not consistently suggest that low dose ibuprofen is associated with an increased risk of cardiovascular events
  - The existing prescribing information reflects the known level of cardiovascular and other risks for these medicines.

Recent Actions by the EMA- Diclofenac

- Data from previous reviews indicated that diclofenac, particularly at high dose, may be associated with an increased risk of arterial thrombotic events such as MI or stroke.
- The evidence to date seems to consistently point towards a less favourable CV risk profile compared to naproxen and ibuprofen, and similar risks as those of Cox-2 inhibitors.

Recent Actions by the EMA- Diclofenac (2)

- June 2013: Following a more in-depth review of diclofenac, EMA recommends new measures to minimize CV risk for diclofenac
  - The effects of systemic diclofenac on the heart and circulation are similar to those of selective COX-2 inhibitors, particularly when diclofenac is used at a high dose and for long-term treatment.
  - Recommendations have been made that the same precautions already in place to minimise the CV thrombotic risk with selective COX-2 inhibitors should be applied to diclofenac.

Acknowledgements

- NSAIDs and CV thrombotic risk safety issue team
- Robert Levin, MD
- Rajdeep Gill, PharmD
- Hina Mehta, PharmD

Non-steroidal Anti-inflammatory Drugs and Thrombotic Cardiovascular Events

Findings from Epidemiological Studies

Joint Meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee
February 10-11, 2014

Andrew D. Mosholder, MD, MPH
Medical Officer
FDA Center for Drug Evaluation and Research
Office of Pharmacovigilance and Epidemiology
Division of Epidemiology II

- Purpose: Describe the recent epidemiology literature regarding nonsteroidal anti-inflammatory drugs (NSAIDs) and the risk of thrombotic cardiovascular (CV) events

- Methods
  - Scope: English-language pharmacoepidemiology publications on NSAIDs and thrombotic CV events
  - Formal literature search by FDA Medical Librarians Joyce Kitzmiller and Gwendolyn Halford , covering 8/2006-8/2011
  - Supplemented by less formal review of other recent literature
  - Findings summarized by topic
  - Examples provided

NSAIDs and Thrombotic CV Event Risk

Specific questions explored in literature review

1. Does thrombotic CV risk vary by compound?
2. Is risk present from the start of NSAID treatment?
3. Are there patient subgroups who are more vulnerable to risk?
4. Do higher dosages convey more risk?
5. Is risk observed at nonprescription NSAID dosages?
6. Is NSAID use associated with stroke?
7. What is the effect of concomitant aspirin on thrombotic CV risk?

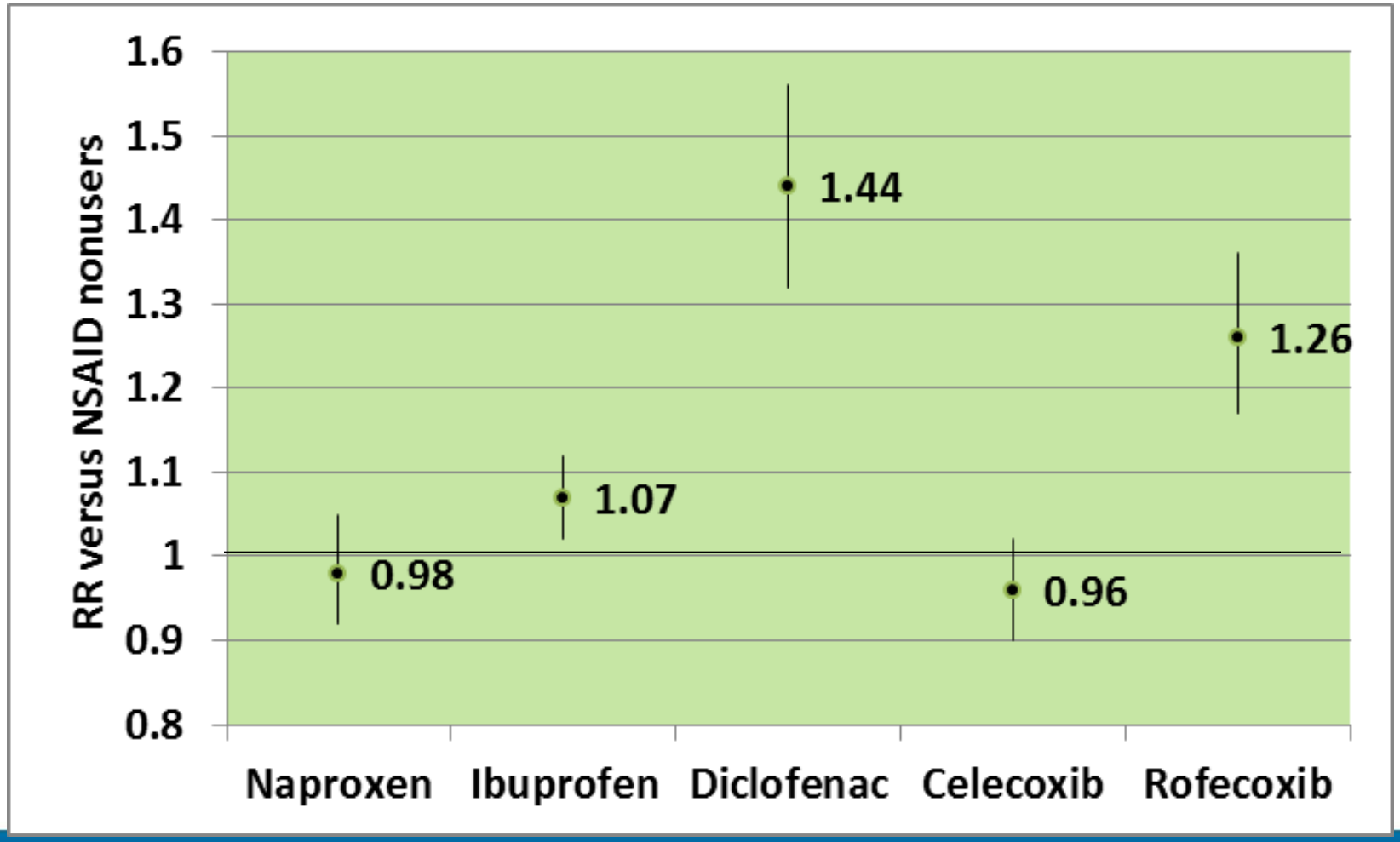
1. Does thrombotic CV risk vary by compound?

1. Does thrombotic CV risk vary by compound?

- Findings from epidemiology studies vary
- More data are available on frequently used NSAIDs
- In general, some frequent patterns across studies:
  - Lower thrombotic CV risk estimates: naproxen
  - Higher thrombotic CV risk estimates: diclofenac, rofecoxib
- Risk estimates reflect not only the compound but the doses at which it was used in the study
- Differences in CV risk estimates by compound could reflect use by different types of patients
  - Hence, need to examine datasets where treatment randomized

Summary Relative Risk Estimates For Myocardial Infarction (MI) from 16 Observational Studies of NSAIDs

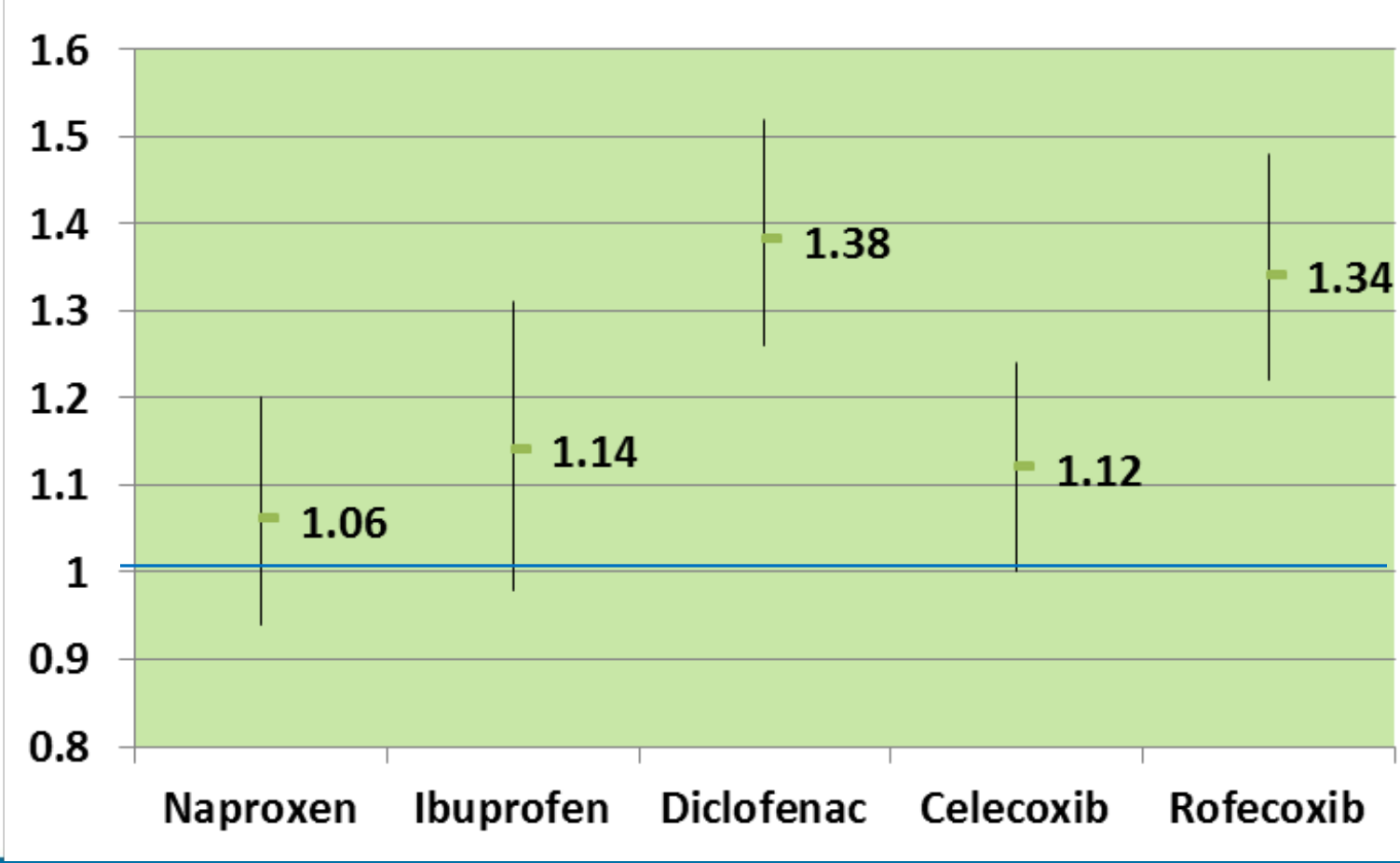
(Hernandez-Diaz et al., Basic Clin. Pharmacol. Toxicol., 2006)



Summary Relative Risk Estimates for MI with Frequently Used NSAIDs: SOS Meta-analysis of 25 Observational Studies

(Varas-Lorenzo et al. Pharmacoepidemiol. Drug Saf. 2013)

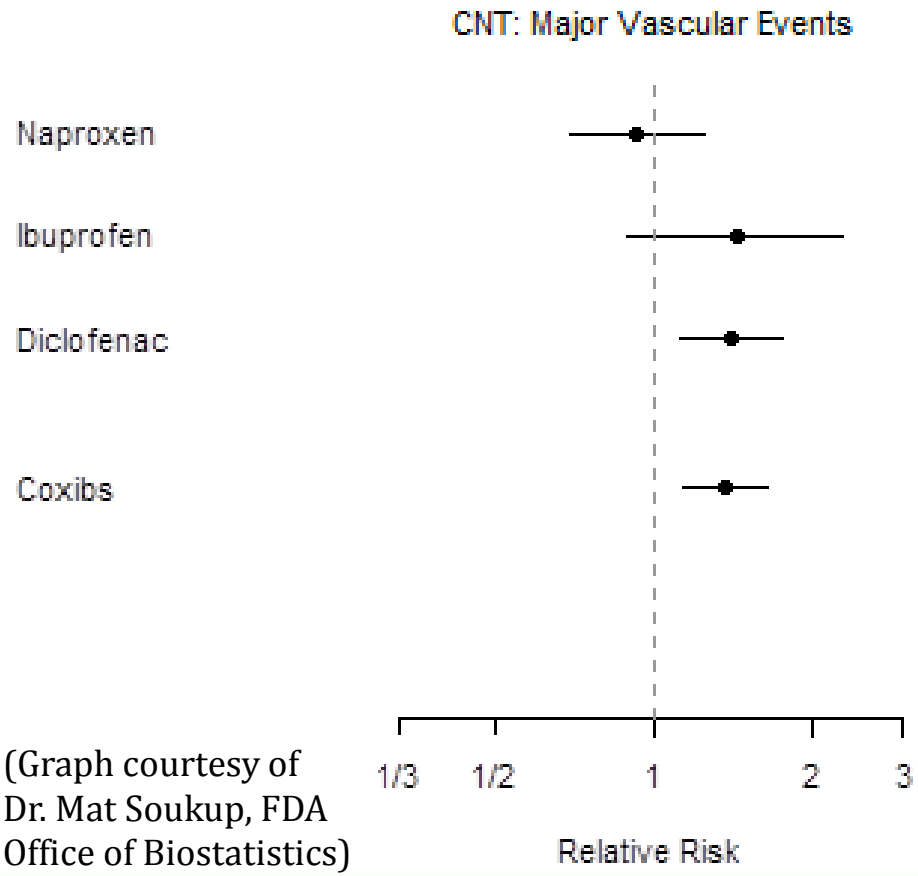
(reference: nonusers or remote NSAID users)

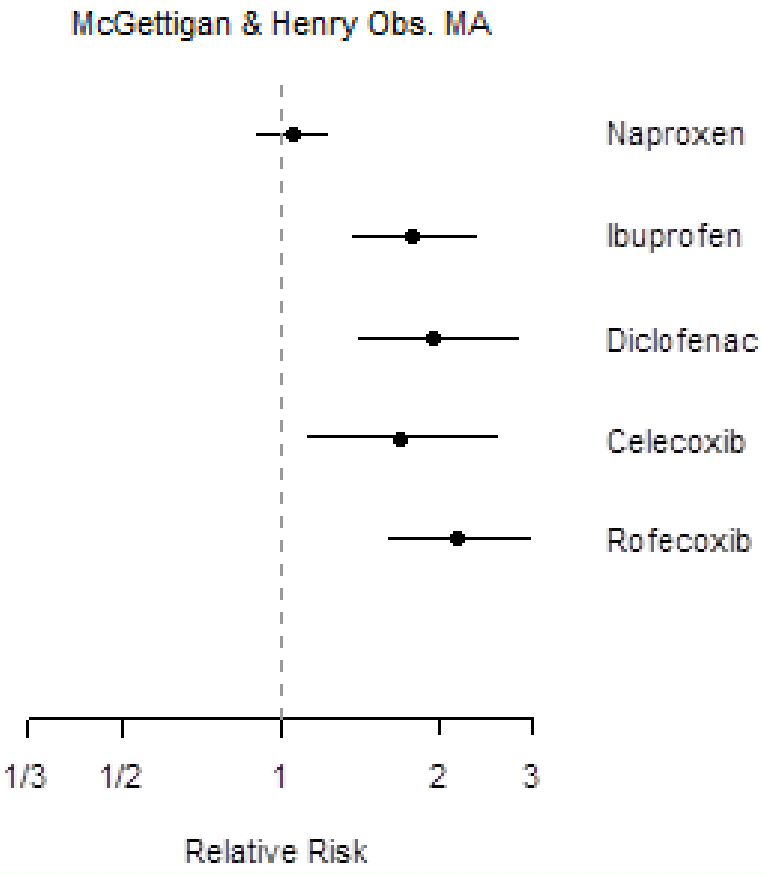


Risk Estimates by Compound for Higher Dose Levels

RR versus placebo, CNT clinical trial meta-analysis (CNT Collaboration, Lancet 2013)

RR for CV events versus nonuse or remote use: observational study meta-analysis (PLoS Med. 2011)





(Graph courtesy of Dr. Mat Soukup, FDA Office of Biostatistics)

1. Does thrombotic CV risk vary by compound?

- Evaluation is confounded by dose, however:
- Lesser risks generally seen with naproxen

2. Is risk present from the start of NSAID treatment?

2. Is risk present from the start of NSAID treatment?

- Various time courses for CV risk reported
- Different mechanisms may operate at different times (Grosser et al. 2006)
  - Platelet aggregation, reduced vasodilation→ immediate risk
  - Atherogenesis, vascular remodeling→ long term risk
- McGettigan and Henry (PLoS Med 2011) reported that in their systematic review of NSAID observational studies, 9 out of 12 studies analyzing new users of NSAIDs showed elevated cardiovascular risk in first month
- For comparison, two clinical trials of coxibs given for 10-14 days after coronary artery bypass grafting (CABG) found an increased risk of MI and stroke (see NSAID class labeling)

Observational Studies of NSAIDs Finding No Latency of Thrombotic CV Risk

Initial time period associated with CV risk	Population	Outcome Risk estimate (CI)	NSAIDs showing increased CV risk	Reference
5.8 days (first quartile for duration of use)	Quebec residents ≥66 y.o., no past MI	Hospitalized MI RR=1.70 (1.26-2.31)	Rofecoxib	Levesque et al. 2006
1 week	Danish, Post MI	Death or re-MI HR=1.45 (1.29-1.62)	Multiple	Schjerning Olsen et al. 2011
1-2 weeks	Finnish adults	First MI OR=1.39 (1.23-1.58)	Not separated	Helin-Salmivaara et al. 2006
1 month	Australian veterans	Hospitalized MI IRR=1.31 (1.12-1.53)	Not separated	Pratt et al. 2010

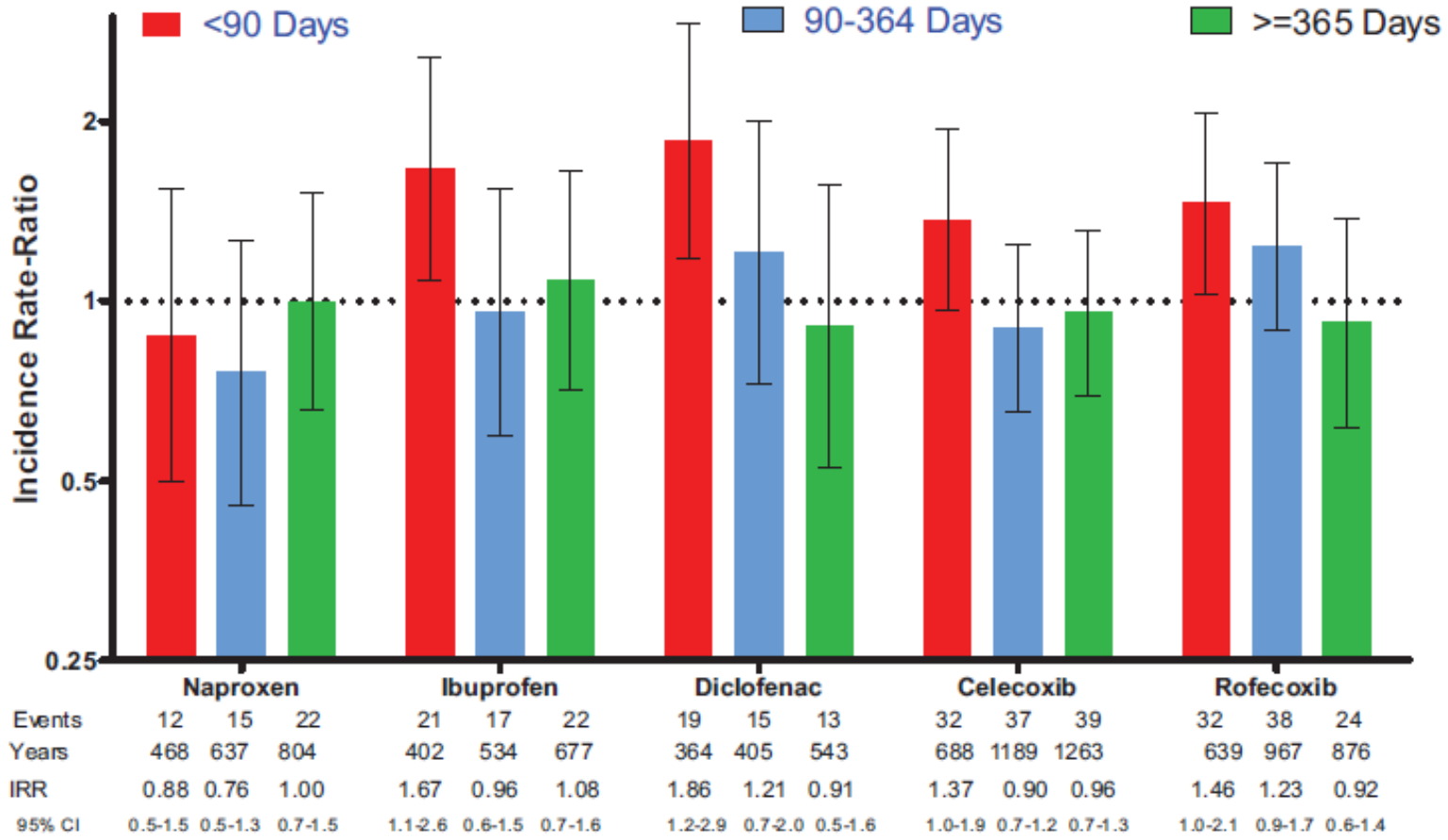
RR rate ratio, HR hazard ratio, OR odds ratio, IRR incidence rate ratio

Observational Studies of NSAIDs Finding No Latency of Thrombotic CV Risk (continued)

Initial time period associated with CV risk	Population	Outcome Risk estimate (CI)	NSAIDs showing increased CV risk	Reference
1 month	Canadians without CV disease	MI or coronary death OR nap=2.84 (1.43–5.63) OR ibu=2.49 (1.12–5.53)	Naproxen & ibuprofen	Varas-Lorenzo et al. 2009
1 month	40-84 y.o. with no CV disease, UK	MI HR=3.43 (1.66--7.07)	Coxibs	Hammad et al. 2008
60 days	Penna. Medicare	Hospitalized MI or ischemic stroke RR=1.14 (1.01–1.29)	Rofecoxib	Solomon et al. 2006
1st prescription	40+ y.o., UK	MI RR=1.23 (1.15–1.31)	Traditional NSAIDs	van Staa et al. 2008

RR rate ratio/relative rate, HR hazard ratio, OR odds ratio

Multinational Cohort of 48,566 Patients Recently Hospitalized for Myocardial Infarction, Revascularization, or Unstable Angina, Outcome= MI or Coronary Death (Ray et al., 2009)



	Naproxen			Ibuprofen			Diclofenac			Celecoxib			Rofecoxib		
Events	12	15	22	21	17	22	19	15	13	32	37	39	32	38	24
Years	468	637	804	402	534	677	364	405	543	688	1189	1263	639	967	876
IRR	0.88	0.76	1.00	1.67	0.96	1.08	1.86	1.21	0.91	1.37	0.90	0.96	1.46	1.23	0.92
95% CI	0.5-1.5	0.5-1.3	0.7-1.5	1.1-2.6	0.6-1.5	0.7-1.6	1.2-2.9	0.7-2.0	0.5-1.6	1.0-1.9	0.7-1.2	0.7-1.3	1.0-2.1	0.9-1.7	0.6-1.4

Figure. Occurrence of coronary heart disease by total duration of NSAID current use. Reference category is nonuse of any NSAID.

Case-control Study of MI in Finland

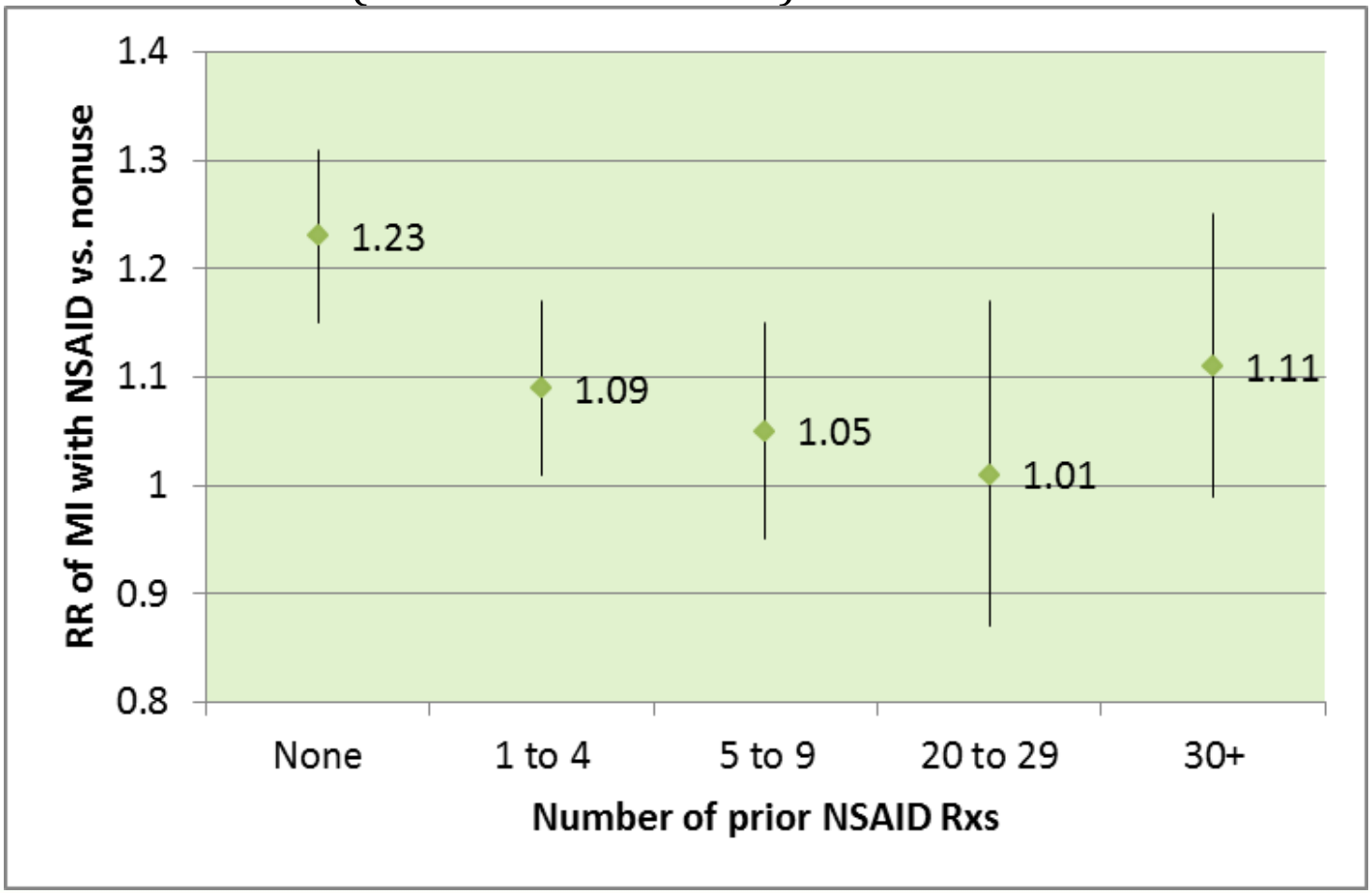
(Helin-Samivaara et al. Eur Heart J 2006)

Table 4 Risk of first time MI among current users of NSAIDs stratified by the duration of continuous therapy (days) in categories

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Non-users	20 645	92 524	1.00 (Reference)	1.00 (Reference)
Any NSAIDs				
1–14	542	1 509	1.55 (1.39–1.73)	1.39 (1.23–1.58)
15–30	436	1 344	1.37 (1.22–1.54)	1.22 (1.06–1.40)
31–90	670	1 807	1.43 (1.29–1.58)	1.25 (1.11–1.41)
91–180	631	1 551	1.74 (1.57–1.93)	1.54 (1.36–1.74)

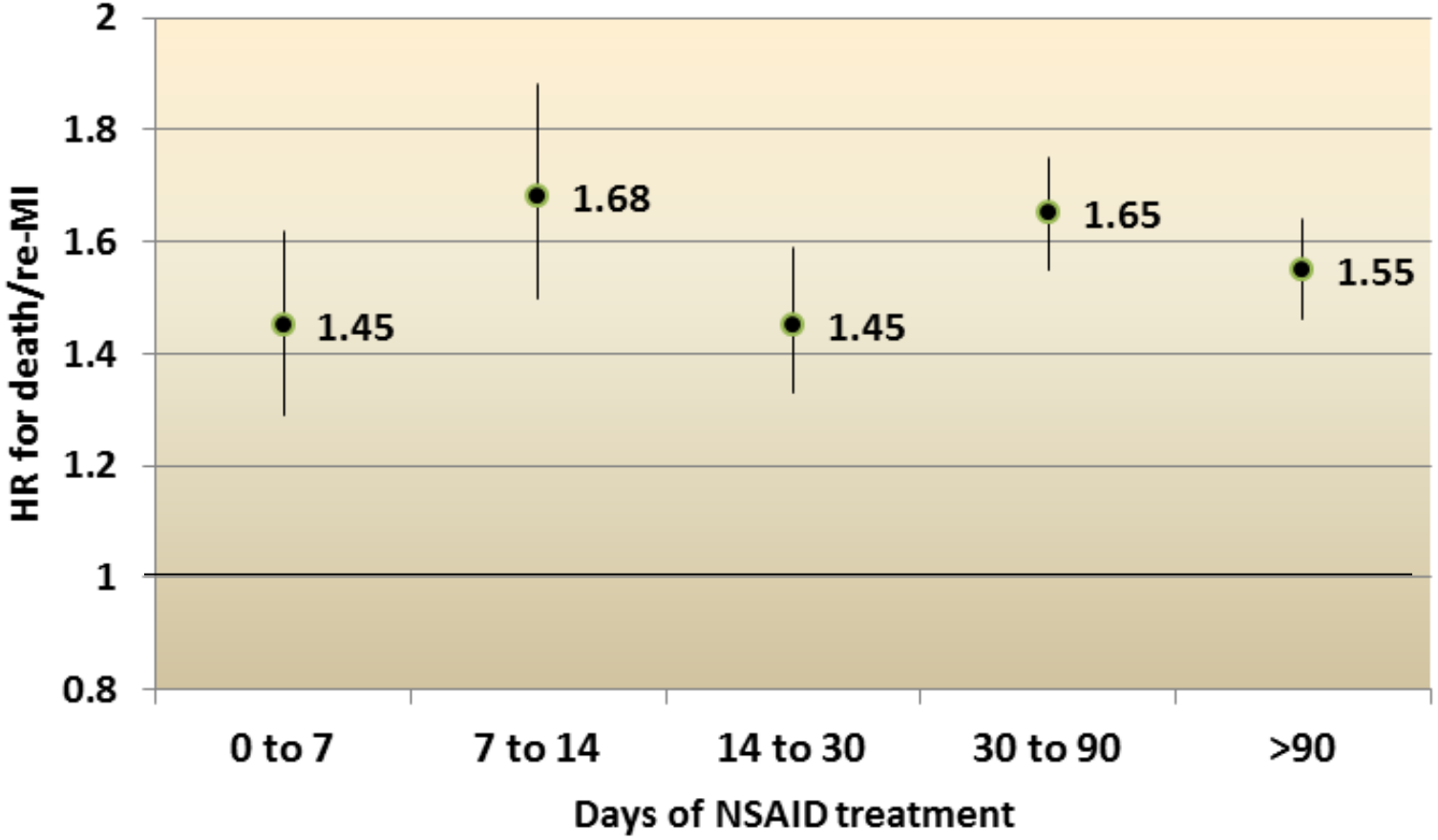
Risk of MI with Traditional NSAIDs by Number of Prior NSAID Rxs, General Practice Research Database

(van Staa et al. 2008)



Risk of Death/Re-MI Associated with NSAID Treatment Population: Danish Post-MI Patients

(Source: Schjerning Olsen et al. Circulation 2011)



2. Is risk present from the start of NSAID treatment?

- Risk is observable from start of NSAID treatment

3. Are there patient subgroups who are more vulnerable to risk?

- Post MI
- Heart failure
- Hypertension
- Other CV risk factors

3. Are there patient subgroups who are more vulnerable to risk?

- Absolute risks substantially higher for vulnerable patients
- Relative risks appear similar for high CV risk vs. healthy patients
- Clinically relevant increases in cardiovascular events with NSAIDs observable both in vulnerable populations and apparently healthy populations

Example of Similar Relative Risks in Different CV Risk Groups, VA & Medicare Claims Analysis, Outcome = MI

(Abraham et al., Aliment.Pharmacol.Ther. 2007)

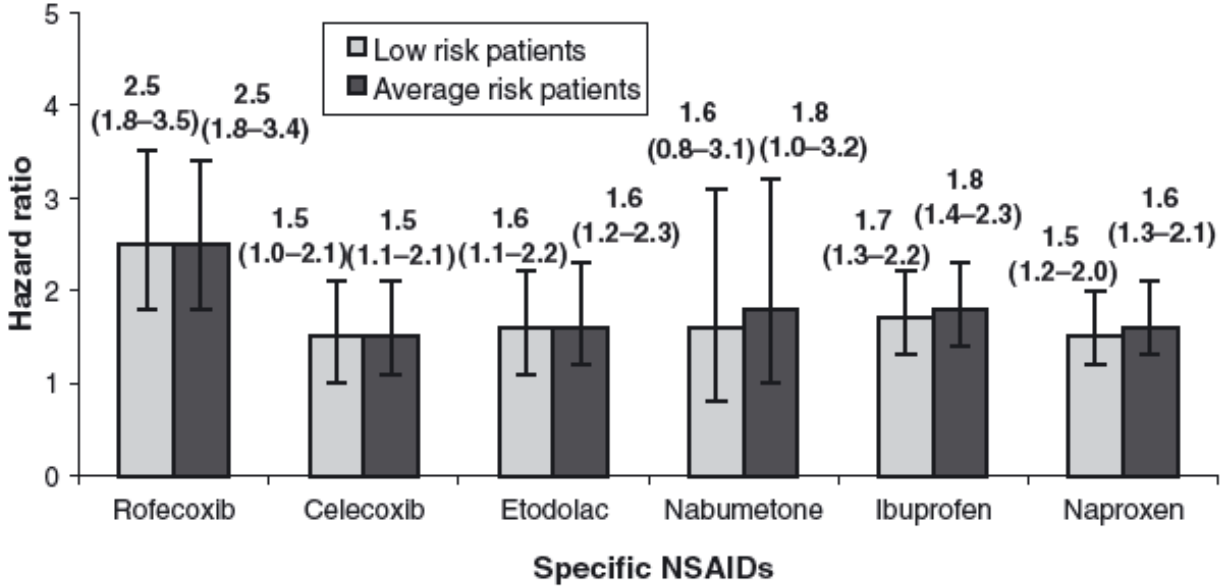


Figure 3. Multivariate analysis examining specific-NSAIDS and risk of MI among average and low-risk patients.
* Where reference category is periods of no NSAID exposure. NSAID, non-steroidal anti-inflammatory drug; and MI, myocardial infarction. Analysis of low-risk patients excludes patients with a history of MI or revascularization procedures, and those with concomitant anticoagulant or anti-platelet agent use.

Estimated Person-years of NSAID Use Associated with One Excess Death (any cause), by Compound and Patient Characteristics (unadjusted) (Danish National Healthcare Data)			
Compound	**Post-MI patients**	**Heart failure patients**	**Healthy individuals**
Rofecoxib	13	9	24
Celecoxib	14	14	24
Diclofenac	24	11	104
Ibuprofen	45	53	446
Naproxen	n.a.	51	1329

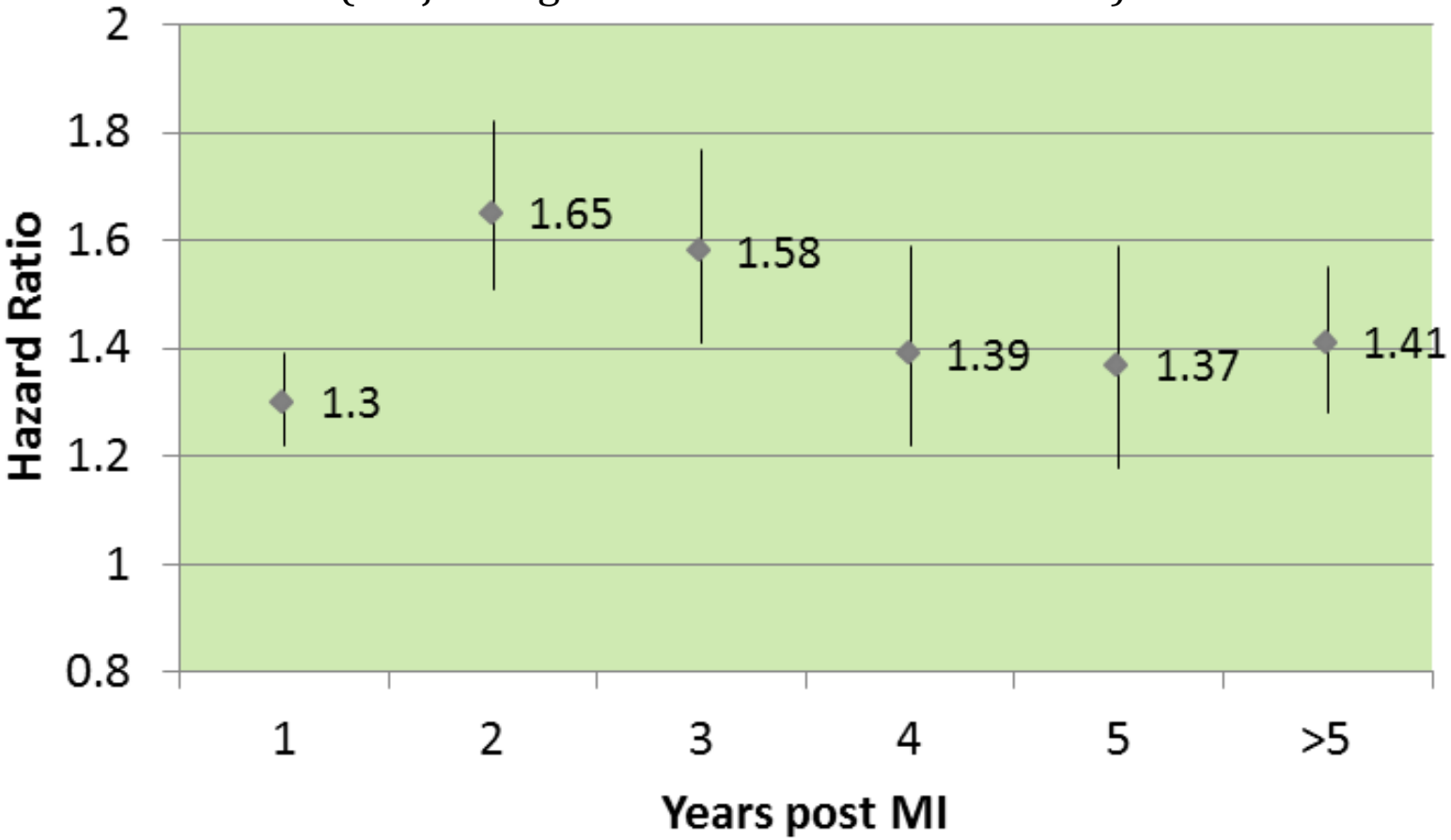
Sources: Gislason et al., Circulation 2006; Gislason et al. Arch Intern Med 2009; Fosbøl et al. CPT 2009

Excess Risks For Serious or Fatal CV Events Observed in Vulnerable Populations

Study	Sample	Outcome	Excess risk with NSAID use
Bavry et al. Am J Med. 2011	Subjects in antihypertensive drug trial, >50 years old, with stable atherosclerotic disease	Cardiovascular death	1 per 100 person-years (unadjusted)
Kohli et al. Am J Med. 2013	Registry of patients ≥45 years old, with stable atherosclerotic disease, or risk factors	Cardiovascular death/MI/stroke	61 after 4 years (=1 per 244 person-years) (adjusted)
Olsen et al. PLoS One 2013	Post-MI patients, Danish national healthcare data	Cardiovascular death	1 per 48 person-years (unadjusted)

Coronary Death or MI Hazard Ratios During NSAID Treatment, in Post-MI Patients, by Year After MI, Danish National Health Data

(Schjerning Olsen et al. Circulation 2012)



3. Are there patient subgroups who are more vulnerable to risk?

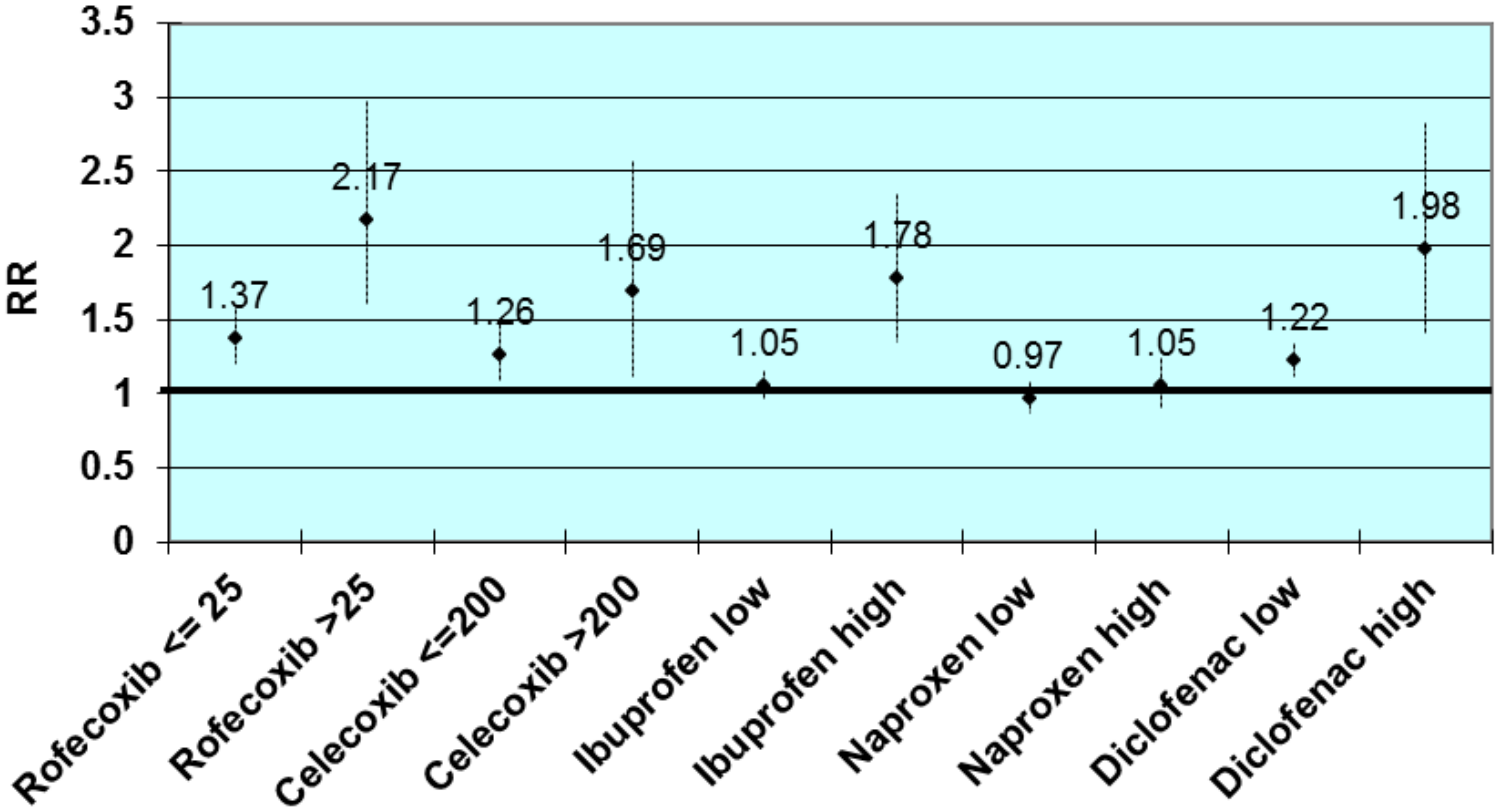
- Vulnerable patients experience more CV events, but CV events are also increased in healthy individuals

4. Do higher dosages convey more risk?

4. Do higher dosages convey more risk?

- From 8/2006 to 8/2011, 15 published observational studies analyzed CV risk by NSAID dose
- 12/15 showed evidence of dose-relatedness for CV risk
- Randomized clinical trial meta-analyses have shown CV risk dose dependency for celecoxib
- Hypothesized that naproxen's anti-platelet activity could produce inverse dose response (greater CV risk at lower dose) (CNT, Lancet 2013)
  - No study showing that pattern was identified

Summary relative risk estimates by dose, serious cardiovascular events, observational study meta-analysis
(McGettigan and Henry, PLoS Medicine 2011)



4. Do higher dosages convey more risk?

- Higher dosages are observed to convey greater risk

5. Is risk observed at nonprescription NSAID dosages?

Nonprescription NSAID doses

Ibuprofen ≤ 1200 mg/d

Ketoprofen ≤ 75 mg/d

Naproxen ≤ 660 mg/d

5. Is risk observed at nonprescription NSAID dosages?

Ibuprofen ≤ 1200 mg/d

- In 2006-2011 literature search, nonprescription ibuprofen dosages analyzed in 9 studies, all from outside US
  - OTC use difficult to determine in US
- 7 of 9 studies found some evidence of positive CV risk with nonprescription ibuprofen doses
  - Sources: Denmark 4, GPRD 1, Taiwan 1, The Netherlands 1
- CV risk estimates often consistent with dose response (i.e., prescription doses had higher risks estimates)
- Some Danish data indicated paradoxical reduction in mortality (confounding or healthy user effect?)

Risk of MI by Ibuprofen Dose in General Practice Research Database (GPRD)

(van Staa et al. J.Intern.Med.(GBR) 2008)

Population and source	Outcome	Reference	Relative risk for MI by mg/day of ibuprofen	
			Mg/day	RR (95% CI)
Age 40+ years GPRD	MI	Past NSAID use	<1200	1.18 (1.01-1.36)
			1200	1.15 (1.05-1.24)
			1201-2399	1.38 (1.17-1.62)
			>=2400	2.16 (1.16-4.01)

Nonprescription NSAID Doses (continued)

- **Ketoprofen ≤ 75 mg/d:** No data
- **Naproxen ≤ 660 mg/d:**
  - 2/5 studies in 2006-2011 literature search analyzing low-dose naproxen found increased CV events
    - MI in patients with heart failure
    - Stroke in a healthy sample
  - ADAPT RCT for dementia prevention: naproxen 440 mg/day
    - Events of CV death/MI/stroke/ CHF/ TIA increased versus placebo
      - HR 1.63, 95% CI 1.04–2.55
    - Limitation: trial halted early

    (ADAPT Research Group, PLoS Clinical Trials 2006)

Nonprescription NSAID Doses (continued)

- More recently, 3 Danish studies (Fosbøl et al. 2012, Olsen et al. 2013, Lindhardsen et al. 2013) analyzed CV events with nonprescription doses of ibuprofen and naproxen.
  - Only associations: ischemic stroke (ibuprofen); hemorrhagic stroke (naproxen)

- Overall, CV risks with nonprescription NSAID doses appear lower than with prescription doses, but elevated risks observed in some studies

5. Is risk observed at nonprescription NSAID dosages?

- CV risk appears lower at nonprescription doses, but is still observable

6. Is NSAID use associated with stroke?

6. Is NSAID use associated with stroke?

- Perhaps less common than MI
  - Ratio of MI:Stroke outcomes roughly 2:1 in APPROVe trial (Baron et al. Lancet 2008)
  - In CNT meta-analysis
    - Less pronounced MI:Stroke imbalance
    - statistically significant association for MI/CHD death, but not stroke
- Observational studies in 2006-2011 literature review showed stroke to be associated with both coxibs and traditional NSAIDs (including naproxen)

Stroke (continued)

- Study of Australian veterans (Caughey et al. Med J Austr 2011)
  - Increased absolute risk of 13.4 stroke hospitalizations/1000/year with initiation of NSAID
  - Risk estimates by compound were generally higher for hemorrhagic than ischemic stroke

- Danish national database study of stroke with NSAID use by apparently healthy individuals (Fosbøl et al. Int J Stroke 2012)
  - Increased ischemic stroke with high dose ibuprofen and diclofenac
  - Increased hemorrhagic stroke with naproxen and diclofenac

6. Is NSAID use associated with stroke?

- Stroke is associated with NSAID use in observational studies

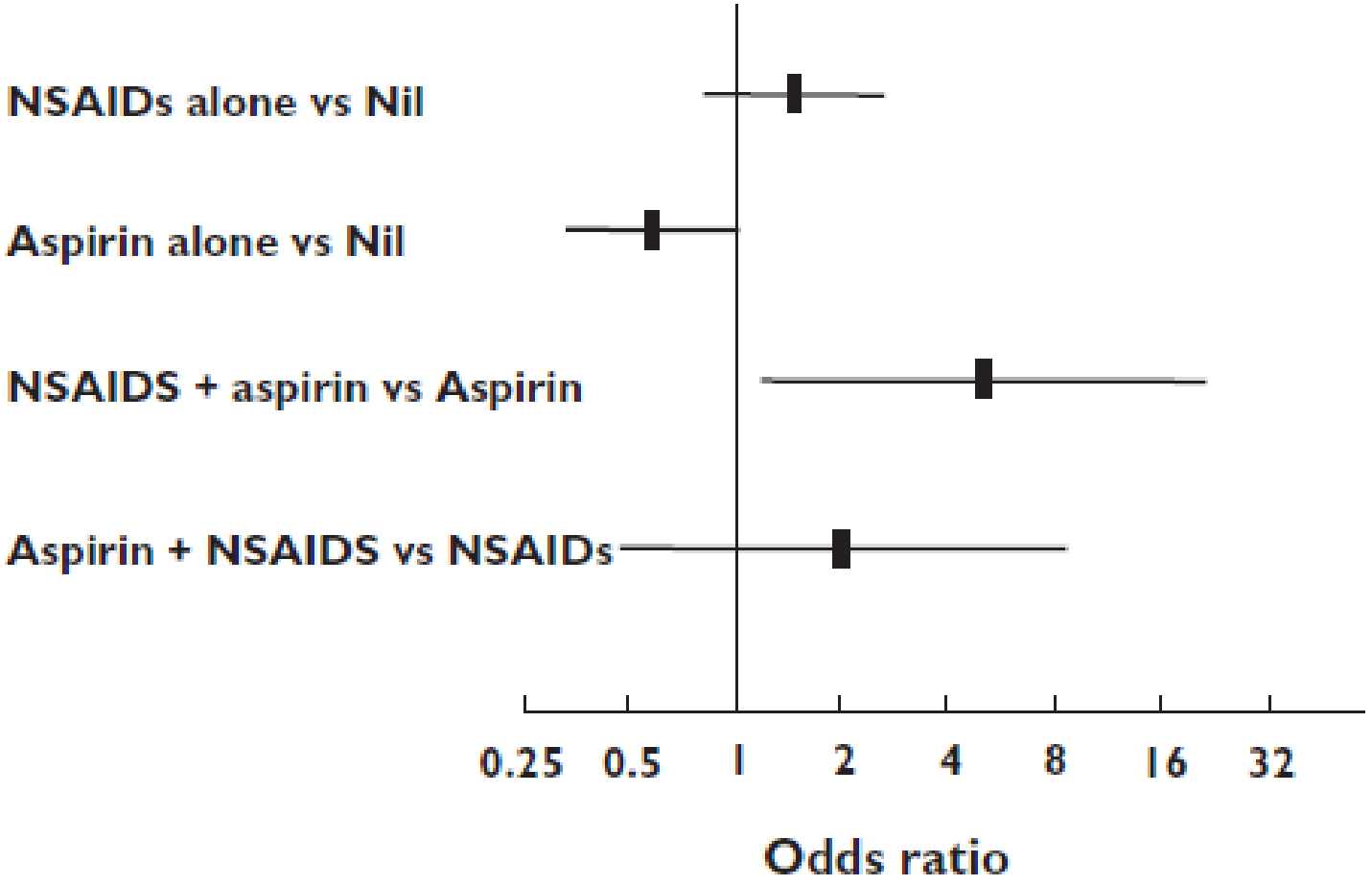
7. What is the effect of concomitant aspirin on thrombotic CV risk?

7. What is the effect of concomitant aspirin (ASA) on thrombotic CV risk?

- Few data on antiplatelet agents other than ASA
- ASA appeared to ameliorate CV risk of NSAIDs in some, but not all, studies
- Evidence that naproxen and ibuprofen can interfere with ASA cardioprotection
  - Consistent with clinical pharmacology of compounds when co-administered
    - (i.e., if ASA not taken ≥2 hrs before ibuprofen/naproxen)
  - CV risk with ibuprofen in absence of ASA observed in one study (van Staa et al., J.Intern.Med. 2008)
    - Suggests interference with ASA cardioprotection does not fully explain ibuprofen CV risk

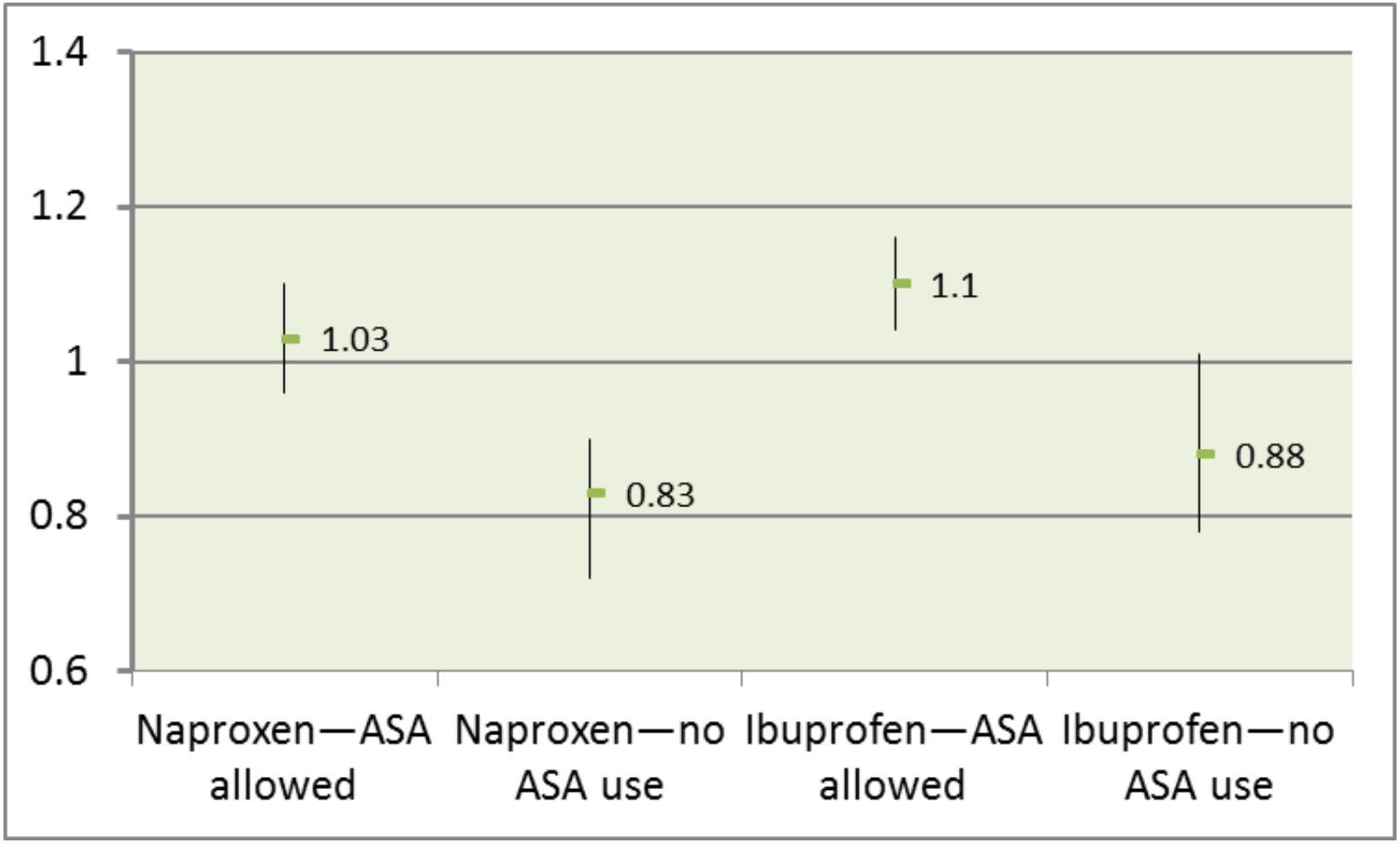
ORs for Nonfatal MI by ASA Use in a Case-control Study

(Source: Figure 2, Hawkey et al., Br J Clin Pharmacol 2006)



Summary MI Relative Risk Estimates from 16 Observational Studies of Nsaids, by ASA Use

(Hernandez-diaz Et Al., Basic Clin.Pharmacol.Toxicol. 2006.)



7. What is the effect of concomitant aspirin on thrombotic CV risk?

- Naproxen and ibuprofen interfere with ASA cardioprotection
- Mixed findings regarding
  - cardioprotective effect of naproxen without ASA
  - ASA amelioration of NSAID-related CV risk

Epidemiology Literature Review: Limitations

- Limitations
  - "A mile wide and an inch deep"
  - Fewer data on less commonly used compounds
  - Generalizations possible, but results not uniform across studies
  - Modest size of risk estimates in majority of observational studies (i.e., RR<2)
    - However, similar in size to RRs obtained from clinical trial data
  - Confounding possible in non-randomized datasets (next slide)

- Confounding: always possible in non-randomized data
  - Garcia Rodriguez et al. (Circulation 2004) found highest risk for MI among patients using NSAID for ill-defined chest pain (suggests protopathic bias)
  - Unadjusted analysis of ibuprofen use in Denmark found higher death rates from both cardiovascular and non-cardiovascular causes (Lipworth et al. Am J Ther. 2004), suggesting confounding by indication
  - Dose, choice of compound may be confounded if not randomized
- How to contend with confounding?
  - All observational studies presented employed regression analysis to address confounding
  - Some studies estimated the degree of confounding needed to fully explain results
  - Important to consider evidence from datasets where treatment randomized

Epidemiology Literature Review: Strengths

- Observational studies can overcome some limitations of RCTs
  - Greater sample sizes
  - Different doses
  - Subjects with a wider variety of characteristics than those in RCTs

Conclusions
Review of Published Epidemiology Data on NSAID Thrombotic CV Risk (slide 1 of 2)

- Risk by compound
  - Confounded by dose
  - Lesser CV risks generally seen with naproxen
    - Perhaps not for stroke
- Risk can be observed without latency period
- Patient vulnerabilities
  - Absolute risks much higher for vulnerable patients
  - Relative risks may be similar for healthy versus high-risk patients
  - Risk can be seen in apparently healthy population
- Risk appears dose-related

Conclusions (slide 2 of 2)

- Nonprescription doses:
  - Ketoprofen—no data
  - Naproxen & ibuprofen: CV risk appears less at nonprescription doses, but still observable in some studies
- Stroke: associated with NSAID use in observational studies
- Aspirin:
  - Naproxen and ibuprofen can interfere with ASA cardioprotection
  - Mixed findings regarding a cardioprotective effect of naproxen without ASA
  - Mixed findings regarding ASA amelioration of NSAID-related CV risk

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FDA BACKUP SLIDES SHOWN

Drug Facts – Selected Warnings

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs

(aspirin, ibuprofen, naproxen, or others)

- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Drug Facts – continued

Do not use

- right before or after heart surgery

Ask a doctor before use if

- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin (ibuprofen only)
- the stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
- you are taking a diuretic
- you have problems or serious side effects from taking pain relievers or fever reducers

Drug Facts – continued

Ask a doctor or pharmacist before use if you are

- under a doctor's care for any serious condition
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than

directed or for longer than directed

Med Guide

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

- **NSAID medicines may increase the chance of a heart attack or stroke that can lead to death**. This chance increases:
- with increasing doses of NSAID medicines
- with longer use of NSAID medicines
- in people who have heart disease
- **NSAID medicines should never be used right before or after a heart surgery called a “coronary artery bypass graft (CABG)."**

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

What are the possible side effects of NonSteroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:

- heart attack
- stroke
- high blood pressure
- heart failure from body swelling (fluid retention)
- kidney problems including kidney failure
- bleeding and ulcers in the stomach and intestine
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- liver problems including liver failure
- asthma attacks in people who have asthma

From Box

- **<u>Cardiovascular Risk</u>**
- **NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. [*see Warnings and Precautions* (5.1)]**
- **Tradename is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. [*see Contraindications* (4)]**

Warnings **5.1 Cardiovascular Thrombotic Events**

- Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with NSAIDs, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

- There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAIDs use. The concurrent use of aspirin and NSAIDs such as diclofenac, does increase the risk of serious GI events *[see Warnings and Precautions (5.2)]*.

5.5 Congestive Heart Failure and Edema

- Fluid retention and edema have been observed in some patients taking NSAIDs. Use Tradename with caution in patients with fluid retention or heart failure.